

Message

From: Kraft, Andrew [/O=EXCHANGELABS/OU=EXCHANGE ADMINISTRATIVE GROUP (FYDIBOHF23SPDLT)/CN=RECIPIENTS/CN=4A94A4F199B247778ABB02285A51B927-KRAFT, ANDREW]
Sent: 10/16/2017 10:53:44 AM
To: Morgan, Daniel (NIH/NIEHS) [E] [morgand@niehs.nih.gov]
CC: Glenn, Barbara [Glenn.Barbara@epa.gov]
Subject: Re: Clarification of NTP report (released in August, 2017)

Thank you, Dan, that is very helpful contextual information.

Thanks again for sharing and best of luck with your ongoing research.

Best,
-Andrew

From: Morgan, Daniel (NIH/NIEHS) [E] <morgand@niehs.nih.gov>
Sent: Friday, October 13, 2017 10:15 AM
To: Kraft, Andrew
Cc: Glenn, Barbara; Morgan, Daniel (NIH/NIEHS) [E]
Subject: RE: Clarification of NTP report (released in August, 2017)

Hi Andrew,

Hope you are doing well. Selection of an 8-week exposure duration was based upon both scientific and practical considerations. The formaldehyde study was initially planned to be a collaborative effort between NIEHS and the EPA in Research Triangle Park; however, the exposure chambers at the EPA inhalation facility were only available to us for 8 weeks. Based upon the HSPC doubling time, the high exposure concentrations used, and the availability of exposure chambers, the 8-week exposure duration was selected. A study protocol was approved and signed. However, after a number of bureaucratic delays, the decision was made to conduct the studies at the NIEHS inhalation facility using the same approved protocol.

In a dose-range-finding study, significant necrosis, squamous metaplasia, and regeneration of respiratory epithelium was present in the nasal cavity after exposure for 2-weeks to 5, 10, and 20 ppm FA. Body weights were decreased by 7% and 12% in mice exposed to 10 and 20 ppm, respectively. Based upon the 2-week study data, exposure to a high concentration of 15 ppm for 8 weeks was expected to be close to the MTD.

Exposure for 8 weeks to 7.5 and 15 ppm FA significantly decreased body weight gain of mice indicating that an MTD was attained in this time period. Although a longer exposure may have been more acceptable, the amount of squamous metaplasia and keratin deposition in the nose after only 8-weeks suggests that the potential for FA to penetrate the nasal tissue and contact with HSPC cells would continue to decrease with longer exposure durations.

I hope this information is helpful. Please call me if you need further clarification or more information. Thanks.

Dan
(919) 541-2264

From: Kraft, Andrew [mailto:Kraft.Andrew@epa.gov]
Sent: Thursday, October 12, 2017 1:38 PM
To: Morgan, Daniel (NIH/NIEHS) [E] <morgand@niehs.nih.gov>

Cc: waalkes@mail.nih.gov; Glenn, Barbara <Glenn.Barbara@epa.gov>

Subject: Clarification of NTP report (released in August, 2017)

Dear Drs. Morgan and Waalkes,

As you are probably aware, the IRIS Program at EPA is conducting a human health assessment of inhaled formaldehyde. Barbara Glenn and myself are the co-chemical managers. A key focus of the assessment is on the carcinogenic potential of formaldehyde exposure. The research report from your division that was released in August titled, "Absence of formaldehyde-induced neoplasia in TRP53 haploinsufficient mice exposure by inhalation" has been brought to our attention and I was hoping that you might be able to provide some clarifying information now that it is publicly available (I spoke with you at your poster on this study at SOT several years back).

The primary reason I wanted to contact you relates to the selected exposure duration of 8 weeks. Acknowledging that rat models were not available, and as you noted in your report, mice appear to be less sensitive to the potential carcinogenicity of formaldehyde, both in terms of exposure level and duration (e.g., including the amount of time after exposure starts before tumors begin to appear, but noting that although it would be ideal if the examinations were longer than 1 year, I understand that this was constrained by background tumors in these mice). In addition, I noticed that all of the previous carcinogenicity studies using these mice that were cited in the report employed exposure durations longer than 26 weeks (most were 35-40 weeks). Can you provide any additional explanation for the 8 week exposure duration than what is already in the report (e.g., about the HSPC doubling time)? I did notice in the report that, at least at 15ppm, you indicated that the maximally tolerated cumulative dose appeared to be 8 weeks; were the exposures intentionally ceased at that point of the study?

Thank you for any explanation, clarification, or insight you can provide. If it would be easier to discuss over the phone, Barbara and I would be happy to give you a call.

Otherwise, I hope that you are settling into Fall, and that your research (or retirement) is going well. I look forward to hearing from you.

Best regards,
Andrew

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